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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/674,387 | 10/01/2003 | Yoshihide Iwaki | 2870-0266P | 4434 |

2292 7590 07/26/2006

BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

| EXAMINER | |
|---|---|
| KAPUSHOC, STEPHEN THOMAS | |
| ART UNIT | PAPER NUMBER |
| 1634 | |

DATE MAILED: 07/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/674,387 | IWAKI ET AL. | |
| | Examiner | Art Unit | |
| | Stephen Kapushoc | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05/15/2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *12-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Claims 1-24 are pending.
Claims 12-24 are withdrawn.

This Office Action is in reply to applicants' correspondence of 05/15/2006. Applicants' arguments have been fully considered but are not found to be persuasive. This Action is made FINAL.

It is noted that in Applicants Remarks (top of page 2) Applicant has indicated that claims 1-12 are under examination. However, pursuant to Applicants' election of 12/23/2005 claim 12 is in fact withdrawn.

### *Claim Rejections - 35 USC § 102*

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-7, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Newton et al (1997) US Patent 5,595,890.

Regarding claim 1, Newton et al teaches methods for the detection of variant nucleotide sequences using two types of allele specific primers (one primer of a particular sequence corresponding to each particular allele); the reference indicates that by particularly selecting the sequence of the allele specific primer it is possible to selectively achieve primer extension of either a variant or normal sequence (Fig. 1; col.2 ln.66 – col.3 ln.6). Because the selected primers specifically amplify the selected target allele, the amount of amplified product resulting from each primer will be based on the amount of the primer used, and thus will be substantially the same if the amounts of

primer in the initial PCR are the same, as in the examples provided in the reference (col.30 ln.25).

Regarding claim 2, Newton et al teaches that the polymorphic position of the analyzed nucleic acid sequence corresponds to the terminal nucleotide of the diagnostic primer (col. 3 ln.18), and specifically provides examples of primer pairs in which the polymorphic position corresponds to the 3' terminal nucleotide of the primers (col.24 lns.24-32), which is within 4 nucleotides of the 3' terminus of the primer.

Regarding claim 3, Newton et al teaches the use of diagnostic primers that contain artificial mismatches (i.e.: mismatches that are in addition to those mismatches present when an allele-specific primer hybridizes to its non-cognate allele target sequence) to increase the specificity of allele specific primers (col.11 lns.52-55; col.12 lns.27-46; col.29 lns.17-35). The reference teaches that an additional mismatch may be positioned 1 base from the terminal mismatch (col.12 ln.31), which would be adjacent to the 3' terminal polymorphism site.

Regarding claim 4, Newton et al teaches that different mismatches in allele specific primers have different hybridization characteristics and thus creates different levels of specificity (col.12 lns.9-22). The reference also teaches that the best design of any particular primer can be determined by experimentation based on such criteria. Such design would include the selection of particular artificial mismatched nucleotides that provide the best specificity for any give allele specific primer.

Regarding claims 5-7, Newton et al teaches the analysis of SNP sites using polymerase reactions such as PCR (col.30 lns.32-47), and the analysis of the products of the reaction by electrophoresis (col.14 lns.27-32; col.30 lns.48-55).

Regarding claim 11, Newton et al teaches allele specific primers can be used for analysis of homo/heterozygosity (col.12 lns.38-42; col.13 lns.35-41; col.21 lns.42-56; Fig.1).

***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al (1997) US Patent 5,595,890 in view of Durward et al (1998).

Regarding claim 1, upon which claims 8 and 9 are dependent, Newton et al teaches methods for the detection of variant nucleotide sequences using two types of allele specific primers (one primer of a particular sequence corresponding to each particular allele); the reference indicates that by particularly selecting the sequence of the allele specific primer it is possible to selectively achieve primer extension of either a variant or normal sequence (Fig. 1; col.2 ln.66 – col.3 ln.6). Because the selected primers specifically amplify the selected target allele, the amount of amplified product resulting from each primer will be based on the amount of the primer used, and thus will

be substantially the same if the amounts of primer in the initial PCR are the same, as in the examples provided in the reference (col.30 ln.25). Newton et al further teaches methods for using allele specific primers to analyze nucleotide variants (col.13 lns.3-41), specifically mentioning point mutations of a corresponding normal sequence (col.15 lns.21-23) (which would include a SNP), and detection via analysis of PCR products.

Newton et al does not teach the analysis of the PCR by-product pyrophosphoric acid (PPi) for the detection step in the analysis of variant nucleotides.

Durward et al teaches a colorimetric method for detecting amplified nucleic acids based on measuring PPi (p.608, right col., lns.23-28). The reference teaches that during the PCR reaction the incorporation of dNMPs from dNTPs into amplified nucleic acids generates inorganic pyrophosphate (PPi, phosphoric acid) in a predicatable 1:1 molar ratio (p.608, right col., lns.18-28; Fig.1). The reference further teaches that PPi can be hydrolyzed to inorganic phosphate (Pi) (p.608, right col., ln.s.31-32), that detection and measurement of Pi is a measure of PCR performance (p.608, right col., lns.33-36), and describe an assay for Pi measurement (p.608, right col., lns.41-52). Durward also provides examples in which amplified DNA is detected by Pi measurement (Fig.2; Fig.3; Table 1). Because the Pi results directly from the hyrdolysis of PPi, this measuring technique is using the PPi.

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have combined the allele specific amplification methods of Newton et al with the phosphate measurement detection methods of Durward et al. One would have been motivated to do so on the assertion of Druward et al that PCR

measurement by phosphate detection can offer advantages in terms of speed and low cost (p.610, left col., lns.35-36). One would have had a reasonable expectation of success because Druward et al provides examples of sensitive and specific detection of PCR performance using the method (Fig.2; Fig.3).

Therefore, in view of the prior art, the claimed invention is prima facie obvious.

5. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al (1997) US Patent 5,595,890 in view of Durward et al (1998) as applied to claims 8 and 9 above, and further in view of Fujisaki at al (1999) US Patent 5,935,520.

The teachings of Newton et al in view of Durward et al are applied to claim 10 as they are applied to the rejection of claims 8 and 9 previously in this office action.

Durward et al teaches detection of PCR performance by measuring the optical density of phosphomolybdenum complex reduced by Fiske-Subbarow reagent.

Newton et al in view of Durward et al does not teach the use of a dry analytical element for the analysis of production of the PCR product.

Fujisaki et al teaches a dry analytical element for analyzing an analyte in a sample solution using a colorimetric reaction (col1. lns.39-50). The reference teaches the use of a reagent layer in the element that contains components necessary for producing a colorimetric reaction.

It would It would have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the methods of Newton et al in view of Durward et al to have included the dry analytical element taught by Fujisaki et al for the

measurement of PCR performance. One would have been motivated to do so based upon the assertion of Fujisaki et al that such dry analytical elements provide for the simple and rapid analysis of sample solutions (col.1 lns.32-37). One would have had a reasonable expectation of success because Fujisaki et al teaches that dry analytical elements can utilize color reaction based assays (col. 1 lns.45-50) in which components necessary for the coloring reaction are contained in a reagent layer (col 8 lns.45-47), and Durward et al demonstrate that the reagents used to create the color change (molybdate and Fiske-Subbadow solution) to measure PCR performance are added sequentially to the PCR mix for the assay (p.609, middle col., lns.10-18).

Therefore, in view of the prior art, the claimed invention is prima facie obvious.

***Response to Remarks***

6. Applicants have traversed the rejection of claims 1-7 and 11 (35 USC 102). The traversal is based on the argument that US Patent 5,595,890 to Newton et al does not disclose the element of designing a primer in order for the amounts of amplification products resulting from each allele-specific primer to be substantially similar (Applicants Remarks, last paragraph, page 3; page 4). Applicants argue that the manner of primer design claimed by independent claim 1 results in amplified product that is substantially the same for each allele, which Applicant asserts is different from the teachings of Newton et al which teaches design of primers to decrease the amount of non-specific amplification product (Applicants Remarks, first full paragraph, page 3). This argument has been considered but is not found persuasive.

7. As written, claim 1 merely requires a method which utilizes 'two types of allele-specific primers' that are designed in such a way that 'the amounts of the amplified product of each of heterozygous alleles are substantially the same'. The claims do not actually recite any particular steps in which the designed primers are used, nor do the claims set forth, for example, any specific actions or method steps that are to be employed in arriving at the primers of the claims. Rather, the claims are sufficiently broad that they encompass the use of primers in a variety of different ways to achieve detection, which primers must merely be 'designed in such a way' that there is at least one way of using the primers that results in product amounts that are 'substantially same'. As Newton et al teach primers that may be used to produce amplification products that are substantially the same for each allele, and further disclose the detection of variant alleles with their primers, the teachings of Newton et al are sufficient to meet the requirements of claim 1. Further, it is noted that Newton et al exemplify the detection of a SNP using primers designed such that the amplification products of each heterozygous allele are substantially the same (Example 4 and Fig 9 of Newton et al).

8. Applicants have traversed the rejection of claims 8 and 9 (35 USC 103 – Newton in view of Durward). Applicants argue that Durward et al does not teach the element of 'allele-specific primers designed in such a way that the amounts of the amplified product of each of heterozygous alleles are substantially the same'. However, Durward was not cited for any teachings of primer design, but for its teaching of amplification detection by pyrophosphoric acid detection. As discussed in the office action of 2/15/2006, and

reiterated in this Office Action, Newton et al provides a method for detection of a SNP using primers designed such that the amplification products of each heterozygous allele are substantially the same. Accordingly, Applicants' arguments regarding Druward et al are not persuasive.

9. Applicants have traversed the rejection of claim 10 (35 USC 103 – Netwon in view of Durward et al and further in view of Fujisaki et al). Applicants argue that neither Durward et al nor Fujisaki et al teach the element of 'allele-specific primers designed in such a way that the amounts of the amplified product of each of heterozygous alleles are substantially the same'. However, as stated above, Durward was not cited for any teachings of primer design, but for its teaching of amplification detection by pyrophosphoric acid detection. Furthermore, Fujisaki et al was not cited for any teachings of primer design, but for its teaching of the use of a dry analytical element. As discussed in the office action of 2/15/2006, and reiterated in this Office Action, Newton et al provides a method for detection of a SNP using primers designed such that the amplification products of each heterozygous allele are substantially the same. Accordingly, Applicants' arguments regarding Druward et al and Fujisaki et al are not persuasive.

***Conclusion***

No claim is allowable. No claim is free of the art.

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire

THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen Kapushoc
Art Unit 1634